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DEVELOPMENT OF FLOATING DRUG DELIVERY SYSTEM FOR LORATADINE: *IN-VITRO* AND *IN-VIVO* EVALUATION

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Keywords:

Gastroretentive, Effervescent, Floating, Extended-release, Controlled release, Direct compression

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ABSTRACT: The reason for this exploration was to develop gastro-retentive drug delivery systems (GRDDS) of loratadine (LTD) to lengthen the gastric residence time (GRT) by using different polymers like hydroxypropyl methyl celluloses (*i.e.,* HPMC K4 M, HPMC K15 M, HPMCK 100 M), xanthan gum and other excipients such as microcrystalline cellulose (MCC), sodium bicarbonate ($NaHCO_3$), magnesium stearate. All LTD floating formulations (F1-F18) prepared by the direct compression technique and evaluated. Fourier Transformed Infrared Spectroscopy (FTIR) studies showed that there are no drug excipient interactions. All LTD effervescent floating matrix tablets (F1-F18) were assessed for various pre-and post-compression parameters like weight variation (mg), hardness (kg/cm^2), thickness (mm), friability (%), drug content (%), *in-vitro* buoyancy (h), *in-vivo* buoyancy (h) and *in-vitro* dissolution (%) and resulted found within pharmacopoeial limits. The drug release and floating property depended upon the polymer type as well as polymer proportions. The floating lag time (FLT) and total floating time (TFT) of all prepared formulations (F1-F18) showed less than 90 seconds and ≥12 hours, respectively. The cumulative percentage (%) of drug release ranged from 57.03 ± 0.13% (F12) to 99.73 ± 0.38% (F5) and optimized formulation (F5) was showed 99.73 ± 0.38% of drug release in 12 h. The *in-vitro* drug release of LTD effervescent floating tablets followed the non-fickian diffusion-controlled release and is best explained by the Korsmeyer-Peppas equation. All the formulations were subjected to various kinetic models, and F5 formulation was optimized as it followed the zero-order kinetics. The optimized formulation (F5) subjected to an *in-vivo* study, and the results of radiographic images shown gastric resident time (GRT) of 4 ± 0.5 hours (n=3). From the *in-vivo* studies it was evident that the GRT increased by floating mechanism.

INTRODUCTION: Oral ingestion is the most favorable, accessible, convenient direction for the administration of healing agents, providing a handy method of successfully achieving both systemic and local effects [1].

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Drug administration's that can be utilized to make systemic delivery of a drug include oral, parenteral, transdermal, buccal, pulmonary, and nasal [2].

No particular routes match every one of the physiological requirements of an ideal absorption site and the relatively oral way is having more suitable characteristics for the absorption of drugs [3]. Among the pharmaceutical dosage forms, oral dosage forms are having a maximum attribute of ideal dosage forms [4, 5]. But poor bioavailability (BA) of orally administered medications is still a challenging one, though extensive advancements in

the drug discovery process are made [6]. But in solid oral dosage forms, drug absorption is not up to the extent of expectation, although this is having good *in-vitro* release patterns [7]. The conventional drug delivery systems provide a specific drug concentration in systemic circulation without offering any or very little control over the release of a drug [8].

The adequate level at the target site can be achieved by alternating administration of unpredictable, excessive doses, often results in constantly changing, which in most situations, and often sub or supratherapeutic plasma concentrations leading to noticeable side effects [9-11]. Controlled release dosage forms (CRDF) provide drug release at a predetermined, predictable over 12 to 24 h period at a regulated rate and that can be taken once or twice a day [12]. It provides numerous benefits compared with immediate-release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater conveniences and higher levels of patient compliance due to a simplified dosing schedule [13].

The major constraint in an oral controlled drug delivery system (CRDDS) is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT) [14]. Some drugs absorbed evenly throughout the digestive tract [15]. Numeral drugs were absorbed in a particular portion of the GIT only or absorbed in various segments of the GIT [16]. These changes in the release may be due to many factors and majorly due to physiological factors like gastrointestinal transit and gastric retention time (GRT) [17-20]. One of the majorities, feasible approaches for achieving a prolonged and predictable drug delivery that offers a new and best option for drug therapy profiles in the GIT, is to control the GRT using gastro retentive dosage forms (GRDF) [21]. That provides a unique and better opportunity for drug therapy [22]. The dosage forms retained in the stomach are called gastro-retentive drug delivery systems (GRDDS) [23]. GRDDS have an absorption window by continuously releasing the medicine for a prolonged period before it reaches its absorption site, thus ensuring its optimal BA [24].

Gastric emptying (GE) of dosage forms is an extremely variable process and emptying time that exists in the stomach for a more extended period than conventional dosage forms [25]. Several difficulties are faced in designing controlled-release (CR) systems for better absorption and enhanced BA [26]. One such problem is the inability to confine the dosage form in the desired area of the GIT [27]. Drug absorption from the GIT is a complicated procedure and is subject to many variables [28]. It is usually acknowledged that the extent of GIT drug absorption is related to contact time with the small intestinal mucosa [29].

Thus, small intestinal transit time is an essential parameter for drugs that are incompletely absorbed [30]. Basic human physiology with the details of motility patterns, physiological and formulation variables affecting the GE was summarized [31-32]. Gastro-retentive systems can remain in the gastric region for numerous hours and hence significantly prolong the GRT of drugs [33]. Prolonged gastric retention improves the solubility for drugs that are less soluble in a high pH environment and reduces drug waste [34]. It has applications also for local drug delivery to the stomach and proximal small intestine [35-36]. Gastro-retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [37-38].

Loratadine (LTD) is a high selectivity for peripheral histamine non-sedating H1-receptors and lacks the central nervous system depressant effects often associated with some of the older antihistamines [39-41]. LTD is class-II drug and used to treat seasonal allergic rhinitis and chronic urticaria [42].

To avoid the above problems associated with oral delivery, we planned to formulate LTD extended-release effervescent floating matrix tablets, and this will allow us to reduce the frequency of administration and enhances patient compliance.

To achieve the goal, different grades of hydroxyl propyl methyl celluloses, xanthan gum, sodium bicarbonate (NaHCO3) and other excipients Microcrystalline cellulose (Avicel PH 200), Magnesium stearate *etc*., were used in the development of LTD effervescent floating tablets.

MATERIALS AND METHODS:

Materials: Loratadine received as a gift sample from Cadila Pharmaceuticals, Ahmedabad, India.

Different grades of HPMC procured from Corel Pharma Chem, Ahmedabad, India. Xanthan gum acquired from Sattvic Innovations, Goa. MCC (Avicel PH 200) obtained from Vasa Pharmachem Pvt. Ltd., Ahmedabad, India. Magnesium stearate purchased from S.D. Fine chemicals Ltd., Mumbai. Hydrochloric acid purchased from Merck specialties Pvt. Ltd., Mumbai, India.

Methods:

Pre-compression Characterization:

Construction of LTD Standard graph: Transfer 100 mg of pure API (LTD) into 100 ml volumetric flask with a few ml of methanol and then make up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/ml (Primary stock solution). 10 ml of this stock is diluted to 100 ml with medium (*i.e.*, 0.1N HCl) to obtain a solution of strength 100 µg/ml (secondary stock solution). From this 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml, 40 µg/ml and 45 µg/ml was prepared [43]. The absorbance's were measured at 280 nm using an ultraviolet (UV) Visible spectrophotometer (Elico, SL210, India) [44-51].

Drug Excipient Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FTIR): The drug excipient compatibility studies carried out by using the KBr disk method and drug test samples of IR spectra recorded between 400 to 4000 cm^{-1} (Star Tech Labs Pvt. Ltd., Hyderabad) [52-55].

Evaluation of a Powder Blend: The powder mixtures of different formulations (F1 to F18) were evaluated for angle of repose (ɵ), bulk density (gm/cm^3), tapped density (gm/cm^3), Carr's index, or compressibility index (%) and Hausner's ratio [56].

'ɵ,' was measured by the fixed funnel method and the below formula used to determine the angle of repose (ɵ).

$$\theta = \text{Tan}^{-1}(h / r)$$

Here 'ɵ' is an angle of repose, 'h' is the height of the pile and 'r' is the radius of the base.

BD = Weight of the sample / Volume of the sample

TD = Weight of the sample / Tapped volume of the sample

The following formulas determined Carr's index or compressibility index (%). Bulk density (BD) and tapped densities (TD).

The following formula calculated Carr's Index

$$\text{Carr's index} = TD\text{-}BT / BD \times 100$$

Hausner's ratios calculated by the following formula.

$$\text{Hausner's ratio} = TD / TB$$

Preparation of LTD Effervescent Floating Matrix Tablets: 10 mg of LTD mixed with the required quantities of polymers (HPMC K4M, HPMC K15M, HPMC K100 M, and Xanthum gum, sodium bicarbonate (10%) and MCC by geometric mixing. The powder blend lubricated with magnesium stearate (1%), and finally, this mixture was compressed by using a 10-station rotary tablet machine (Karnavathi, Gujarat, India) using a 6 mm standard flat-face punches and formulation details given in **Table 1**.

Post-Compression Charac-terization after compression of all prepared floating LTD formulations (F1 to F18), different evaluation tests performed to assess release characteristics of the developed formulations as well as to find out the physicochemical properties [57].

Weight variation (mg): The weight of the whole prepared LTD floating formulations (n=20; randomly from every batch) determined by using an electronic balance (Shimadzu, AUX220, Japan) and calculate the average weight of the tablet [58].

Thickness (mm): The width of the entire prepared LTD effervescent floating formulations (*i.e.*, n=20; randomly from every batch) measured by Vernier calipers and calculate the average thickness [59].

Friability (%): The friability test was performed with prepared LTD floating tablets (n=20; unintentionally from the entire batches) by placing tablets on Raoche firabilator and allowed to make 100 resolutions or operate with 25 rpm speed for 4 min and calculated by following formula [60].

$$\% \text{ Friability} = W_1 - W_2 / W_1 \times 100$$

Where W_1 is the initial weight of tablets; W_2 is the final weight of de-dusted tablets and the values <1% is usually good enough. By this test durability of the tablet can be determined.

Hardness (kg/cm^2): The hardness (n=6; erratically from every grouping after that middling should be deliberate) of the prepared LTD floating tablets were measured by using Pfizer type hardness tester (Dolphin Pharmacy Instruments, Pvt. Ltd., Mumbai). By this test, the tablet mechanical potency or crushing strength recorded [61].

TABLE 1: FORMULATION COMPOSITION OF GASTRORETENTIVE TABLETS OF LORATADINE

CODE (mg/tablet*)	LTD	HPMC			Xanthan gum	MCC (Avicel PH 200)
		K4M	K15M	K100M		
F1	10	20	-	-	-	59
F2	10	30	-	-	-	49
F3	10	40	-	-	-	39
F4	10	-	20	-	-	59
F5	10	-	30	-	-	49
F6	10	-	40	-	-	39
F7	10	-	-	20	-	59
F8	10	-	-	30	-	49
F9	10	-	-	40	-	39
F10	10	-	-	-	20	59
F11	10	-	-	-	30	49
F12	10	-	-	-	40	39
F13	10	-	10	-	10	59
F14	10	-	15	-	15	49
F15	10	-	20	-	20	39
F16	10	-	-	10	10	59
F17	10	-	-	15	15	34
F18	10	-	-	20	20	39

*Total weight of a tablet is 100 mg; 10% of $NaHCO_3$ and 1% of Mg state used in every formulation

Drug Content (%): The prepared LTD floating formulations (n=6; from each batch) were collected at random and pulverized. One tablet weight (*i.e.*, 100 mg) was transferred into 100 ml volumetric flask (VF); to this, 100 ml of methanol added, then the solution subjected to sonicate for up to 2 h. The standard solution (*i.e.*, 0.1N HCl) and drug solution filtered through the Whatman filter paper (*i.e.*). By using UV, visible spectrophotometer samples were analyzed for drug content at 280 nm [62].

***In-vitro* Buoyancy Studies (Hours):** The *in-vitro* floating (n=6) was determined by the reported method. Here, prepared LTD was placed in a 100 ml beaker containing 0.1 N HCl. The time required floating the tablet or rising from the bottom of the beaker to the surface of the glass called floating lag time (FLT), and the total duration of tablet float on the surface is called as total floating time (TFT) [63].

Swelling Index (%): The previously weighed (W_0) prepared LTD effervescent floating tablets were placed in the 100 ml beaker containing 0.1N HCl, and the tablets were removed at the time interval of 1 h for up to 12 h and weighed (W_t). The swelling index can be measured by studying its weight gain due to the uptake of water. Hence, the swelling index was calculated by the following formula to find out the swelling ability [64].

$$\text{Swelling index} = W_t - W_o / W_o \times 100$$

Where W_t is the final weight of tablets at a time't' and 'W_0' is the initial weight of the tablets

***In-vitro* Dissolution (%):** The release rate or in vitro dissolution studies (n=6; from each batch) of LTD effervescent floating tablets carried out in 900 ml of 0.1 N HCl with USP dissolution type - II (*i.e.*, paddle method) apparatus at 75 rpm and maintained at 37 ºC ± 0.5 ºC. About 5 ml of aliquot (*i.e.*, sample) was withdrawn at predetermined time intervals for every 1 h up to 12 h and replaced with 5 ml of fresh medium (*i.e.*, 0.1 N HCl) each time. The samples were analyzed by using a double beam UV visible spectrophotometer (Elico, SL210, Hyderabad) at 280 nm. By using a standard calibration curve of LTD, the cumulative percentage of drug release calculated [65].

***In-vivo* Buoyancy Studies (Hours):** *In-vivo* gastric retention time (GRT) was determined by X-ray procedure in healthy human volunteers (n=3). The method of radiographic studies was approved by the institutional ethical committee (IEC). For the *in-vivo* study *(i.e.*, Proposal no. IRBAGI/2018-19/11), Barium sulfate ($BaSO_4$) containing LTD floating tablets were prepared by a similar method as described in the formulation.

In this revision, part of the amount of LTD was replaced utilizing $BaSO_4$, and other ingredients remain equivalent [66].

Mechanism of Drug Release Kinetics: The drug release data of LTD prepared floating matrix tablets were fitted into different kinetic models representing Zero order, First order, Higuchi, and Peppas model to know the release mechanism [33, 67-69].

RESULTS AND DISCUSSION:

Pre-compression Characteristic Studies:

Standard Graph of LTD: The different concentrations of LTD in 0.1N HCl was scanned and found the maximum absorbance at 280 nm (*i.e.*, λ_{max}) [57, 70-71]. Construction of LTD in 0.1N HCl was plotted by taking concentration ranging from 5 to 45 µg/ml and showed good correlation with a regression coefficient (R^2) value of 0.998 and shown in **Fig. 1**.

Drug Excipient Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FTIR): The spectral laboratory analysis of pure drug (LTD) and optimized formulation (F5) were showed in **Fig. 2** and **Fig. 3** correspondingly, principle peaks at similar wavenumbers, and in the optimized formulation (F5), some different wave numbers observed [72-73].

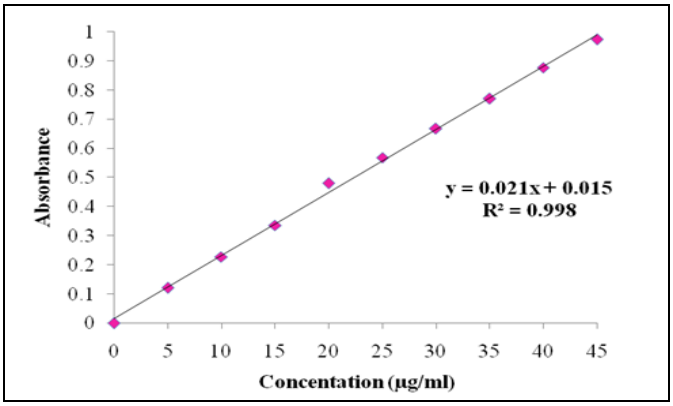

FIG. 1: CALIBRATION CURVE OF LORATADINE

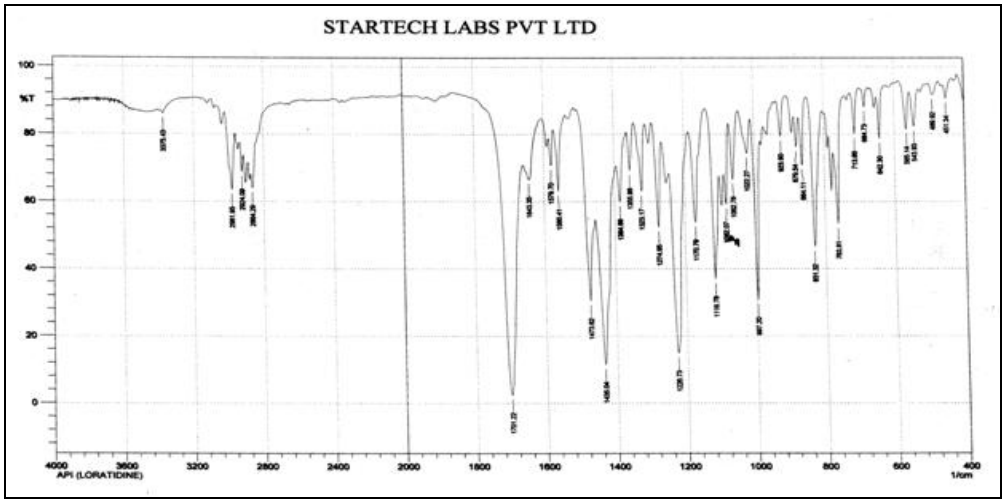

FIG. 2: FTIR SPECTRUM OF PURE DRUG (LORATADINE)

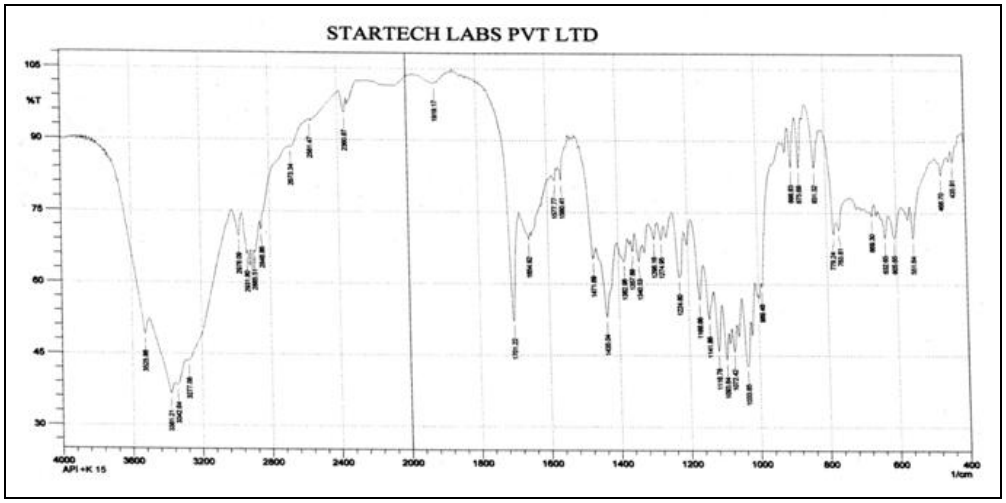

FIG. 3: FTIR SPECTRUM OF OPTIMIZED FORMULATION (F5)

The IR spectra of the pure drug (Loratadine) showed the characteristic absorption peak at 1701 cm^{-1} indicates the presence of C=O. strong absorption band at 3375 cm^{-1} , characteristic band at 2981 cm^{-1} , 2884 cm^{-1} shown in **Fig. 2**.

The IR spectra of the physical mixture of optimized formulation (F5) also showed in **Fig. 3**; the similar bands mentioned above of LTD and however, some additional peaks were observed with physical mixtures, which could be due to the occurrence of polymers. The results advise that there is no relation connecting the drug and excipients used in the current study [57].

Evaluation of the Powder Blend: All prepared LTD powder blends are subjected to various parameters. The angle of repose ranges from 21.34 ± 0.87 (F7) to 29.41 ± 1.08 (F14); Carr's index ranges from 11.02 ± 0.06 (F11) to 14.59 ± 0.81 (F6); Hausner's ratio values ranges from 1.02 ± 1.11 (F9) to 1.33 ± 0.61 (F7). From the above results, the powder blends (*i.e.,* F1 to F18) show that good to excellent flow properties [58].

TABLE 2: PRE-COMPRESSION CHARACTERISTIC STUDY OF LTD FORMULATIONS

Formulation Code	Carr's Index (%)	Hausner's Ratio (%)	Angle of Repose (Θ)
F1	12.36 ± 0.84	1.06 ± 0.62	23.82 ± 0.63
F2	11.06 ± 0.62	1.08 ± 0.98	21.63 ± 0.98
F3	13.68 ± 0.71	1.09 ± 1.30	28.04 ± 0.02
F4	12.49 ± 1.09	1.33 ± 0.61	24.34 ± 0.83
F5	11.08 ± 0.53	1.19 ± 1.10	29.40 ± 1.05
F6	14.59 ± 0.81	1.24 ± 0.83	23.23 ± 0.06
F7	13.72 ± 0.14	1.12 ± 0.62	21.34 ± 0.87
F8	12.08 ± 0.52	1.29 ± 1.13	22.40 ± 1.08
F9	14.15 ± 1.07	1.02 ± 1.11	26.52 ± 1.06
F10	12.08 ± 0.50	1.06 ± 1.08	25.40 ± 1.02
F11	11.02 ± 0.06	1.20 ± 0.74	22.78 ± 0.69
F12	12.09 ± 0.52	1.22 ± 0.84	24.61 ± 0.15
F13	12.79 ± 1.09	1.31 ± 0.62	23.34 ± 0.14
F14	12.08 ± 0.53	1.23 ± 1.08	29.41 ± 1.08
F15	13.79 ± 1.02	1.28 ± 0.61	23.34 ± 0.09
F16	12.38 ± 1.04	1.21 ± 0.54	27.51 ± 1.23
F17	12.36 ± 0.37	1.26 ± 0.99	23.71 ± 0.81
F18	11.54 ± 0.91	1.20 ± 0.38	28.23 ± 1.08

Post-compression Characteristic Studies:

Weight Variation: The total weight of each formulation was maintained constant; the weight variation of the tablets was within the allowable limits of ± 5% as per Indian Pharmacopeia (IP) limits. By using electronic balance for every batch of tablets weighed individually and resulted in the ranges from 96.16 ± 1.73 mg (F8) 100.25 ± 0.60 mg (F10). Based on the above results found, all batches were in the acceptable limits.

Tablet Thickness: Tablet thickness was also used to assess the quality of the tablets. Under normal conditions of manufacture, the total weight of the tablet and thickness were linearly related. The width of floating tablets ranged from 2.53 ± 0.84 mm (F5) to 3.02 ± 0.48 mm (F15) and linearly correlated with the weight of the tablets.

Friability: Friability test results showing all formulations have enough resistance to mechanical shock and abrasion. Drug content uniformity in all formulations was calculated and the percent of active ingredients ranged from 0.11 ± 0.87% (F5) to 0.41 ± 0.35% (F16).

Tablet Hardness: The hardness of the tablet was varies from 5.12 ± 1.06 kg/cm^2 (F6) to 6.20 ± 0.54 kg/cm^2 (F4) and was maintained for all the batches to minimize the effect of hardness on the drug release because; the result of polymer concentration is the only area of interest.

Drug Content: The drug content was estimated by UV visible spectrophotometer, and the drug released from the entire prepared LTD floating tablets ranges from 96.40 ± 0.82% (F13) to 101.03 ± 1.05% (F4).

***In-vitro* Buoyancy Studies:** Further, the formulated tablets evaluated for buoyancy in 0.1 N Hydro-chloric acid (HCl) media.

Sodium bicarbonate ($NaHCO_3$) was added as a gas generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all tablets due to carbonated blend in tablets produced CO_2 that was trapped in the swollen matrix, thus decreasing the density of the tablet <1g/cm^3 making the tablets buoyant. Due to the change in the concentration of different polymers, show different *in-vitro* buoyancy. The floating lag time (< 90 sec.) of the LTD tablet. The floating lag time (FLT) and total floating time (TFT) of all formulations shown in **Table 4.**

TABLE 3: POST-COMPRESSION CHARACTERISTIC STUDIES OF LTD FLOATING MATRIX TABLETS

Formulation Code	*Weight Variation (mg)	*Thickness (mm)	*Friability (%)	$Hardness (kg/cm^2)	$Drug content (%)
F1	97.86±1.62	2.79±0.16	0.12±0.65	5.35±1.56	96.86±0.65
F2	98.98±0.75	2.75±0.73	0.24±1.34	5.29±1.10	98.83±0.21
F3	96.93±1.36	2.86±0.54	0.20±1.14	5.38±1.12	99.31±1.06
F4	96.48±1.07	2.99±0.51	0.17±1.06	6.20±0.54	101.03±1.05
F5	100.01±0.02	2.53±0.84	0.11±0.87	5.79±0.85	99.96±1.06
F6	98.38±0.74	2.64±0.62	0.13±0.76	5.12±1.06	99.85±0.93
F7	98.92±1.07	2.82±0.53	0.12±0.54	5.67±0.62	98.35±1.32
F8	96.16±1.73	2.81±0.78	0.31±0.76	5.25±0.94	100.01±1.43
F9	100.08±0.46	2.75±0.69	0.21±0.56	5.45±1.14	98.31±0.76
F10	100.25±0.60	2.69±0.96	0.23±1.05	6.10±1.43	95.98±1.25
F11	99.28±1.03	2.91±0.64	0.15±1.54	5.61±1.12	98.31±0.36
F12	97.90±1.02	2.94±0.79	0.21±0.56	5.32±1.53	99.81±1.74
F13	96.74±1.98	2.75±0.28	0.14±0.98	5.37±0.58	96.40±0.82
F14	99.35±1.25	2.63±0.51	0.21±1.15	5.27±1.08	98.90±1.09
F15	97.18±2.01	3.02±0.48	0.19±1.08	6.01±1.63	100.03±0.16
F16	100.08±1.03	2.81±0.63	0.41±0.35	5.48±0.59	99.81±1.54
F17	96.99±1.09	2.69±0.56	0.29±0.87	5.67±0.85	96.91±1.07
F18	98.78±0.04	2.87±0.61	0.22±1.25	5.55±0.71	98.25±0.84

*Data represents Mean ± SD (n=20); $ Data represents Mean ± SD (n=6)

TABLE 4: FLOATING PROPERTIES OF LTD TABLETS

*Formulation Code	FLT (sec)	TFT (h)	Swelling Index (%)
F1	89±0.5	≥12	116.82±1.3
F2	81±2.0	≥12	125.79±2.5
F3	76±1.5	≥12	132.18±3.1
F4	81±3.0	≥12	120.45±2.9
F5	76±1.8	≥12	153.26±3.0
F6	70±2.3	≥12	165.18±3.2
F7	75±4.8	≥12	256.25±1.9
F8	68±1.9	≥12	296.74±2.3
F9	59±2.2	≥12	301.68±3.2
F10	64±3.0	≥12	110.93±1.6
F11	58±1.5	≥12	118.36±2.6
F12	52±1.9	≥12	140.92±3.1
F13	60±2.5	≥12	128.16±1.5
F14	56±2.6	≥12	135.74±2.2
F15	48±3.1	≥12	175.14±1.6
F16	58±2.5	≥12	120.92±2.3
F17	53±1.7	≥12	170.53±1.9
F18	48±1.5	≥12	296.5±1.1

* Data represents mean± SD (n=3)

Swelling Index: The percentage of swelling obtained from the water uptake studies of the formulations shown in **Table 4**. Complete swelling was achieved at the end of 8 h and then diffusion and erosion takes place.

The formulation F9 containing HPMC K100M (1:4 drug: polymer) shows the higher swelling compared to that of the formulations containing HPMC K4M, HPMC K15M. The swelling index of the tablets increases with an increase in the polymer viscosity grades.

***In-vitro* Dissolution Test:** The drug release of all prepared effervescent floating LTD was studied by using USP dissolution apparatus II with 900 ml of 0.1N HCl media and maintained at 37± 0.5 ºC with a rotation speed of 75 rpm.

As per predetermined time intervals, Aliquots of 5 ml were collected and replenished with an equivalent volume of fresh medium and analyzed by using a UV visible spectrophotometer at 280 nm.

The *in-vitro* dissolution testing was performed, and the results of the formulations were expressed **Fig. 4** to **Fig. 10**. *In-vitro* dissolution studies of F1 to F3 formulations prepared with HPMC K4 M are unable to extend the drug release for the desired period.

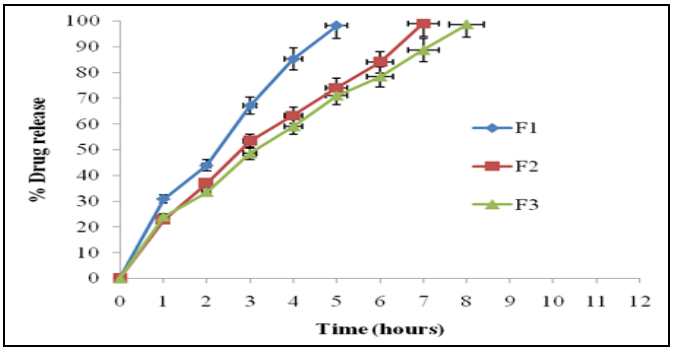

FIG. 4: CUMULATIVE % DRUG RELEASES OF FORMULATIONS WITH HPMC K4M

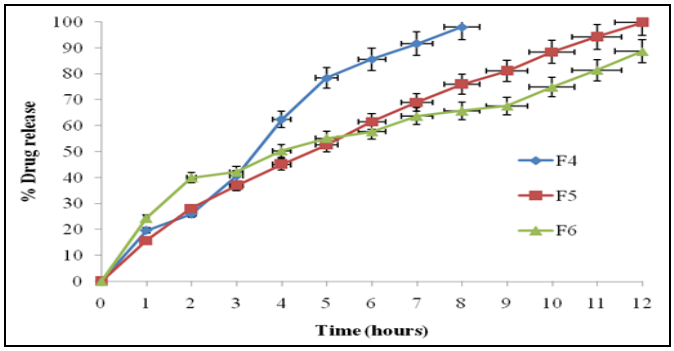

FIG. 5: CUMULATIVE % DRUG RELEASES OF FORMULATIONS WITH HPMC K15M

In-vitro dissolution studies of F4, F5, F6 formulations prepared with HPMC K15M, and the percent of drug release from formulations F5, F6 was found to be 99.73 ± 0.38%, 88.73 ± 0.42% in 12 h respectively. Formulation F4 was unable to extend the drug release desired period. This is because of the change in polymer concentrations used in these formulations. Formulation F5 obtained the desired drug release profile and floated with an FLT of 76 sec.; for these reasons, it was considered as the best formulation. *In-vitro* dissolution studies of F7, F8, and F9 formulations prepared with HPMC K100 M and percent drug released calculated. The results indicated that the drug release was retarded significantly due to high viscous polymers. Comparing the three different grades of methocel (K4M, K15M, and K100M), it was found that methocel K15M provided better-extended release characteristics with excellent drug release in the desired period and good *in-vitro* buoyancy. *In-vitro* dissolution studies of F10, F11, F12 formulations prepared with xantham gum were done in 0.1N HCl, and the percent of drug releases from F10, F11, and F12 was found to be 87.89 ± 1.05%, 79.9 ± 1.53% and 57.03 ± 0.13% in 12 h respectively. It indicated that xantham gum retards the drug release heavily, and floating lag time increased. *In-vitro* dissolution study of F13, F14, F15 formulations were unable to extend the drug release desired period.

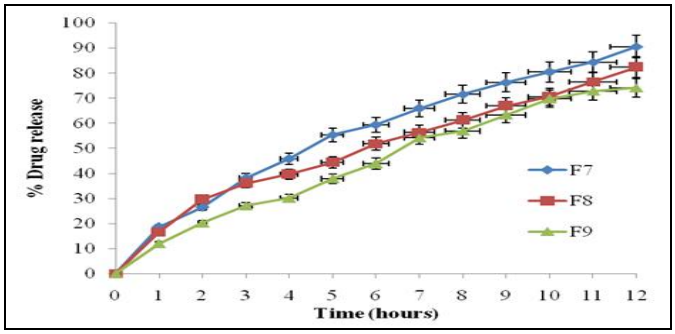

FIG. 6: CUMULATIVE % DRUG RELEASES OF FORMULATIONS WITH HPMC K100M

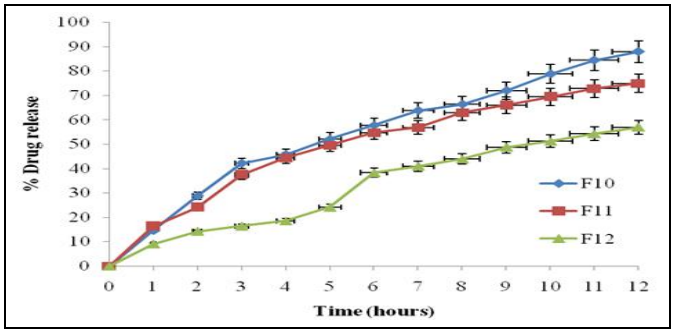

FIG. 7: CUMULATIVE % DRUG RELEASES OF FORMULATIONS WITH XANTHAN GUM

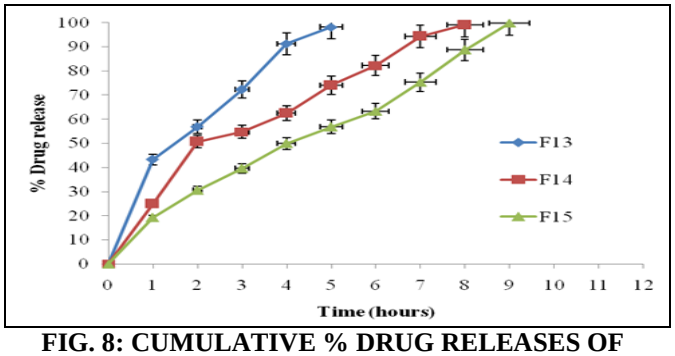

FIG. 8: CUMULATIVE % DRUG RELEASES OF FORMULATIONS WITH HPMC K15M AND XANTHAN GUM

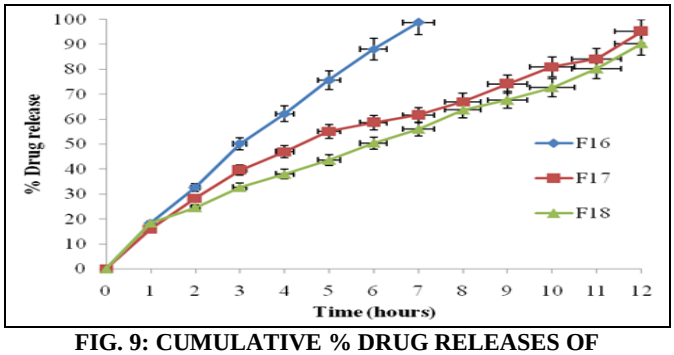

FIG. 9: CUMULATIVE % DRUG RELEASES OF FORMULATIONS USING WITH A COMBINATION OF HPMC K100M AND XANTHAN GUM

In-vitro dissolution study of formulations F16, F17, F18 was done in 0.1N HCl, and the TFT was found to be ≥12 h. F16 formulation was unable to extend the drug release in the desired period.

Kinetic Modelling of Data: The drug release profiles of prepared LTD floating formulations (F1 to F18) were subjected to different kinetic models *viz*. Zero-order, First order, Higuchi and Korsmeyer-Peppas. The majority of the formulations R^2 values of Korsmeyer-Peppas and Zero order models are near to 1, than other kinetic models. The optimized formulation (F5) followed Korsmeyer-Peppas model (R^2 = 0.994) and 'n' value is 0.56 (shown in **Table 5**). Therefore the most probable mechanism that the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion.

***In-vivo* X-ray Study:** *In-vivo* studies were conducted on healthy male human volunteers to find the gastric residence time (GRT) of the tablet for F5 (optimized) formulation. The studies were based on X-ray radiography, and images were taken at different time points to find the location of the tablet shown in **Fig. 10**. The radiograms were chosen for initial (0 h), 2 h, and 4 h, and the tablet remains float on the gastric content for about 6 ± 0.5 h (n=3).

TABLE 5: COMPILATION OF THE RESULTS FROM ALL THE MATHEMATICAL MODELS APPLIED TO THE OPTIMIZED FORMULATION (F5)

Formulation Code	Zero-order	First-order	Higuchi	Korsmeyer-Peppas	'N' Value of Peppas
F5	0.986	0.748	0.823	0.994	0.56

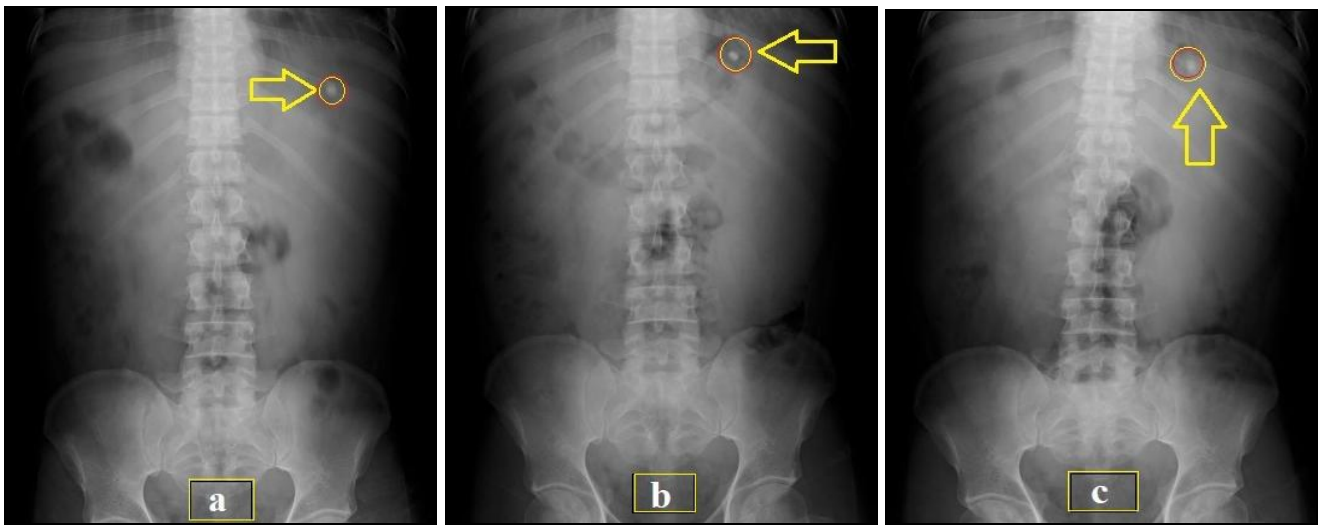

FIG. 10: X-RAY IMAGES OPTIMIZED FORMULATION (F5); a) at Initial; b) at 2 h; c) at 4 h; (n=3, Mean ± SD)

CONCLUSION: Effervescent floating matrix tablets of Loratadine was formulated as an approach to increase gastric residence time (GRT) and thereby improved its bioavailability. Among all prepared formulations HPMC K15M showed better physicochemical properties and retarded the drug release for desired period. *In-vivo* radiographic studies indicated that tablets remained in the stomach for 4 ± 0.5 h, which suggests the increase in the GRT is due to floating and swelling principle. The development of upcoming technologies can be applied for solving problems and it is essential to asses gastro-retentive dosage forms on a case-by-case basis because the physicochemical nature of drug and excipients, types and composition of polymers, drug dose and manufacturability may depend on product specification.

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CONFLICTS OF INTEREST: Nil

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